Conference Report

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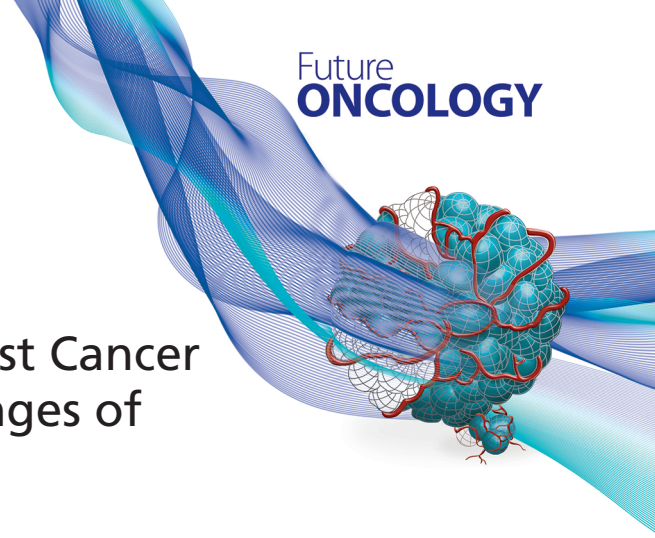

Highlights of the San Antonio Breast Cancer Symposium 2019 Part 2: the challenges of tumor heterogeneity

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First draft submitted: 7 April 2020; Accepted for publication: 18 May 2020; Published online: 29 May 2020

Keywords: hormone replacement therapy • San Antonio • screening • stromal-epithelial interactions

The annual San Antonio Breast Cancer Symposium (SABCS) uniquely combines the principles of multidisciplinary management with the basic science underlying pathobiological processes in breast cancer. The 42nd meeting was held at the Henry B Gonzales Convention Centre in downtown San Antonio, TX, USA on 10–14 December 2019. The symposium delivers a range of presentations covering basic, translational and clinical sciences. Important trials that are potentially practice changing are often presented at SABCS and published concurrently or shortly thereafter. This is the second of a two-part report highlighting important presentations and focuses on topics relating to: extended endocrine therapy; chemoprevention of breast cancer; alternate approaches to adjuvant chemotherapy; anti-HER2 therapies and also immunotherapy with checkpoint inhibitors. Relevant background information is included where context appropriate.

Extended hormonal therapy

With the advent of aromatase inhibitors, hormonal therapy has become increasingly complex and breast cancer patients are no longeroffered the ubiquitous 5 years of tamoxifen therapy irrespective of hormonal status. The optimum schedule for adjuvant systemic hormonal therapy in terms of choice of agent and duration of usage remains uncertain but emerging evidence supports a risk stratified approach with extended schedules of between 7.5–10 years recommended for most patients [1]. It should be noted that there is a significant risk of relapse for many hormone receptor positive breast cancers that persists throughout the first 20 years of follow-up with half of these cases occurring beyond 5 years. Extended adjuvant endocrine therapy with an aromatase inhibitor (AI) or tamoxifen after a standard 5 years of tamoxifen treatment span is associated with an improved disease-free survival, although the optimum duration of AI therapy in these circumstances is unclear. Seven-year results (6.9 months) of the NSABP B-42 trial were presented at SABCS in 2016 [2]. This trial randomized 3966 postmenopausal hormone receptor positive patients to 5 years of letrozole or placebo after 5 years of standard endocrine therapy (AI alone or Tamoxifen [TAM]/AI switch). Although there was a 15% reduction in the primary end point of disease-free survival in favor of letrozole ($p = 0.048$), this was not deemed statistically significant due to adjustment of a predefined two-sided p-value to 0.0418. Eleftherios Mamounas (NRG Oncology, CA, USA) presented updated trial results at 10 years showing a statistically significant reduction in disease-free survival events for letrozole (Hazard ratio [HR]: 0.84; $p = 0.011$) with an absolute decrease of 4%. There was also a 29% decrease in risk of distant recurrence with letrozole (7.5 vs 5.7%) and a 26% reduction in breast cancer-free interval events (13.3 vs 10.3%). Subgroup analysis revealed letrozole to be associated with a significant disease-free survival benefit in: node positive patients; prior tamoxifen users; patients aged ≥60 years; bone mineral density t-score ≤2.0; previous mastectomy. There were no differences in overall survival between groups or rates of adverse events such as osteoporotic fractures (6.5 vs 6.4%)

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and arterial thrombotic events. Extended endocrine therapy may be relevant to hormone receptor positive patients at higher risk of relapse – this includes most premenopausal/postmenopausal women receiving chemotherapy.

Genomic classifiers (Oncotype-DX, PAM50, Endopredict, IHC-4, Breast Cancer Index) may help identify patients at risk of late distant recurrence and who are most likely to respond to extended therapy. However, decisions for extended therapy should also take account of factors such as, patient's age, preference and adherence to prescribed medications together with cost implications within different healthcare systems. Compliance is a potential problem for endocrine therapy with up to one-quarter of patients taking medication intermittently or discontinuing medication early due to musculoskeletal side effects of joint stiffness and pain (occurring in 43 and 47% of patients, respectively). Rates of compliance for aromatase inhibitors is correlated with household net worth and a switch from a brand name to a cheaper alternative increases adherence.

Chemoprevention of breast cancer

The international breast cancer intervention study II was designed to determine if a 5-year pulse of anastrozole therapy can safely and effectively prevent breast cancer in high-risk postmenopausal women. A total of 3864 patients were recruited with 1920 in the anastrozole arm and 1944 placebo cases. Eligibility criteria included: ≥2 relatives with breast cancer; mother or sister with breast cancer <50 years; or mother or sister with bilateral breast cancer [3]. The primary end point for this study is the incidence of invasive or noninvasive breast cancer with the evaluation of overall incidence and for the post 5-year time period. J Cuzik (Queen Mary University of London, UK) provided an update of this trial at a median follow-up of 10.9 years that revealed continuing benefit throughout the second 5 years. Thus, anastrozole halved the incidence of breast cancer overall (HR: 0.50; 95% CI: 0.38–0.65; $p < 0.0001$) with evidence of a greater reduction in the first 5 years (HR: 0.39) but a substantial reduction in the second 5 years. Moreover, the effects of chemoprevention in each 5 year time period were not significantly different and reductions in incidence of invasive disease did not reach significance for hormone receptor negative tumors (ER positive; HR: 0.46; 95% CI: 0.33–0.65; $p < 0.0001$) versus oestrogen receptor (ER) negative (HR: 0.76; 95% CI: 0.39–1.45; $p = 0.4$). Hence, these updated results show a continued impact of anastrozole on breast cancer incidence after stopping treatment at 5 years and there may be potential advantages of using an aromatase inhibitor over tamoxifen for chemoprevention because fewer women need to be treated with anastrozole for 5 years to prevent one breast cancer (29 vs 49 women). Yet chemoprevention (i.e., the use of drugs to reduce breast cancer risk) has not been widely adopted into clinical practice. This might be attributable to failure of trials to show any reduction in mortality despite several chemopreventive agents having been shown to reduce the incidence of breast cancer.

Alternate adjuvant systemic chemotherapy

Results from the open labeled multicenter Phase III Create-X trial were presented at SABCS in 2016 and have since been published [4]. This Japanese-Korean study examined adjuvant capecitabine after neoadjuvant chemotherapy (NACT) in partial responders.

A total of 900 non-pCR or node positive, HER2-negative patients were randomized following surgical treatment to either control or oral capecitabine on days 1–14 (repeated 3 weekly for eight cycles). Patients with residual disease after induction chemotherapy are more likely to relapse and it remains unclear whether further postoperative (adjuvant) chemotherapy can improve survival. Patients within this trial received a spectrum of standard neoadjuvant schedules containing anthracyclines and/or taxanes. The primary end point was disease-free survival with secondary end points of overall survival, safety and cost–effectiveness. The study reported statistically significant improvement in both disease-free (HR: 0.70; 95% CI: 0.53–0.93; one-sided $p = 0.00524$) and overall survival (HR: 0.60; 95% CI: 0.40–0.92; one-sided $p < 0.01$). Side effects were minimal with slight increase of neutropenia and diarrhea and compliance high. The investigators concluded that further investigation of postoperative capecitabine and cost–effectiveness analysis is justified despite multiple negative studies for addition of capecitabine in the adjuvant setting.

Following publication of the Create-X study, there has been a persistent uncertainty about which triple negative breast cancer (TNBC) patients with residual disease will benefit from adjuvant capecitabine. The Create-X study recruited patients from oriental populations that may have intrinsic genetic differences influencing response to what was an 'eclectic range' of chemotherapy regimens within this trial. Patients with residual disease after NACT have a higher chance of relapse but it remains unclear whether any prolongation of survival with postoperative chemotherapy can be justified in terms of side effects and added costs. Against this background, the German Breast

Group have undertaken a meta-analysis of individual patient data from 12 randomized trials involving capecitabine as adjuvant (three-quarters) or NACT.

Mvan Mackelenberg (University Medical Center, Schleswig-Holstein, Keil, Germany) reported on this meta-analysis of 15,457 patients enrolled in trials involving both TNBC and other subtypes. The primary objective was to determine the effect of capecitabine on disease-free survival with overall survival a secondary outcome. In particular, this large meta-analysis aimed to ascertain whether there was any interaction between capecitabine-specific toxicity and treatment effect. There was no overall improvement in disease-free survival except for those trial designs where capecitabine was an 'additional' agent to any standard chemotherapy schedule (HR: 0.888). This hazard ratio was only significant for the end point of disease-free survival in respect of the Create-X trial, proclaiming benefit from addition of capecitabine. When analysis was confined to TNBC, there were benefits for disease-free survival from addition of capecitabine to other systemic treatments (HR: 0.818) but once again this was only statistically significant for a minority of trials (Create-X and FinXX). It was concluded that capecitabine can be considered as adjuvant therapy for TNBC patients with residual tumor after NACT but further prospective trials of TNBC are required that incorporate both capecitabine and platinum agents (carboplatin).

M Toi (Kyoto University Hospital, Japan) presented results from the Japanese Phase III POTENT trial investigating whether addition of an oral derivative of biochemically modified fluorouracil (S-1) can enhance standard adjuvant systemic therapy. The trial recruited almost 2000 patients from 130 institutions in Japan with stage I–IIIB hormone receptor positive, HER2-negative breast cancer deemed to be at intermediate to high risk of recurrence. The combination of S-1 with endocrine therapy as adjuvant treatment for hormone receptor positive, HER2-negative breast cancer was associated with an increase for invasive disease-free survival of approximately 5%. At a median follow-up of 51.4 months there were significantly more cognate events in the control (15.9%) than S-1 (10.6%) arms (HR: 0.63; p = 0.0003). Addition of this agent led to an increase in grade 3–4 diarrhea and neutropenia but these adverse effects are likely to be offset by improved efficacy in selected higher risk hormone receptor positive patients for whom conventional chemotherapy is not considered optimal therapy. Use of multigene assays may help identify those patients likely to derive greatest benefit from this novel agent.

Anti-HER2 directed therapies

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of the HER2/neu growth factor. Overexpression of HER2/neu occurs in approximately 30% of invasive breast cancers and is associated with a worse prognosis [5]. When combined with taxane-based chemotherapy for management of advanced breast cancer, trastuzumab improved time to disease progression (4.6 vs 7.4 months) [6]. Clinical trials have confirmed improvements in both disease-free and overall survival. Two American trials reported a reduction in risk of recurrence of about 50% from at least 12 months of trastuzumab treatment and show a sustained and robust survival benefit favoring anti-HER2 therapy with more prolonged follow-up (despite some issues of patient cross-over after publication of initial trial results) [7,8]. Despite dramatic responses to anti-HER2 therapies in both early and advanced disease settings, most patients with metastatic HER2-positive breast cancer will eventually progress due to development of either *de novo* disease or resistance.

Several strategies have been devised for improving survival outcomes in HER2-positive disease that aim to more effectively inhibit the HER2 signaling pathway. One approach is dual-blockade using pertuzumab that targets a different epitope of HER2 and interferes with homo- and hetero-dimer formation and in turn disrupts intracellular signal transduction pathways. Functional redundancy within these more distal elements can potentially be overcome with combinatorial therapies in which agents such as CDK4/6 inhibitors or P13K/AKT/mTOR inhibitors are added to anti-HER2 therapy. Tumors associated with infiltrating lymphocytes benefit more from trastuzumab treatment that may modulate the microenvironment and interact synergistically with T cell checkpoint inhibitors. There is a complex relationship between antitumor effector immunity and HER2 that influences the tumor immunosuppressive microenvironment. There is an evidence from preclinical models that CDK4/6 inhibitors can overcome development of resistance to anti-HER2 therapy [9] and clinical studies are evaluating combinations CDK 4/6 inhibitors, trastuzumab, pertuzumab and aromatase inhibitors after standard first-line therapies for metastatic breast cancer (MBC; ClinicalTrials.gov: NCT02947685 and NCT02448420).

The antibody drug conjugate trastuzumab emtansine (T-DM1) also targets the HER2 pathway but acts by inducing mitotic catastrophe after binding to the HER2 receptor and releasing its payload (DM1) that interferes with spindle formation after internalization. T-DM1 was compared with capecitabine and lapatinib in the EMILIA trial which showed an increase in progression-free survival (HR: 0.68) and also an improvement in overall survival. The

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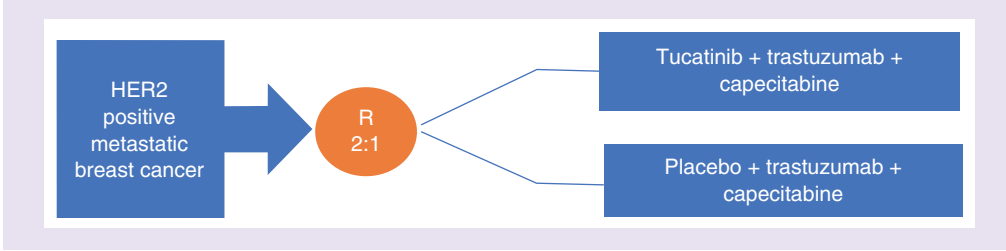

Figure 1. Schematic diagram showing design of the HER2CLIMB study comparing tucatinib with placebo for patients with pre-treated HER2 positive metastatic breast cancer with and without brain metastases. Patients in both arms of the trial received capecitabine and trastuzumab.

Box 1. GS1-01 Tucatinib versus pacebo, both combined with capecitabine and trastuzumab, for patients with pretreated HER2-positive metastatic breast cancer with and without brain metastases (HER2CLIMB).

Trial type
- Study arms
- Inclusion criteria
- Enrollment
- Study dates
- Primary outcomes
- Secondary outcomes

Phase II randomized (2:1), double-blinded controlled trial
- Tucatinib + trastuzumab + capecitabine (n = 410)
- Placebo + trastuzumab + capecitabine (n = 202)
- HER2-positive MBC
- Prior treatment with trastuzumab, pertuzumab and T-DM1
- PS status 0 or 1
- Brain MRI at baseline
- 612 patients
- January 2016–September 2019
- Progression-free survival (CNS and non-CNS)
- PFS in patients with baseline brain metastasis
- Overall survival
- Duration of response
- Clinical benefit rate
- Incidence of adverse events
- Quality of life

Data taken from Murthy *et al.*
Trastuzumab 6 mg/kg (loading dose 8 mg/kg).
Tucatinib 300 mg orally twice daily.
Capecitabine 1000 mg/m^2 PO BID.
CNS: Central nervous system; MBC: Metastatic breast cancer; PFS: Progression-free survival; PS = Performance status.

role of T-DM1 in the metastatic setting was reinforced by results of the Phase III TH3RESA study demonstrating a clinically meaningful improvement in overall survival (median 22.7 months [95% CI: 19.4–27.5] vs 15.8 months [95% CI: 0.54–0.85]) in HER2-positive metastatic patients previously treated with taxane, trastuzumab and lapatinib [9].

In the first general session of the meeting, Rashmi Murthy (MD Anderson Cancer Centre, TX, USA) emphasized that no single therapy represents standard of care for HER2-positive MBC patients previously exposed to trastuzumab, pertuzumab and T-DM1. Up to half of HER2-positive stage IV patients now develop brain metastases as survival is prolonged, although this group of patients are often excluded from clinical trials. The HER2CLIMB study investigated the clinical efficacy of an oral tyrosine kinase inhibitor (TKI) in patients with untreated or previously treated brain metastases. Tucatinib is an investigational TKI that is highly selective for the intracellular kinase domain of the HER2 receptor (Figure 1 and Box 1). More than 600 patients were randomized in a double-blind

placebo controlled, active comparator trial and received either tucatinib or placebo in combination with trastuzumab and capecitabine. Approximately half of these trial patients had brain metastases that were previously treated and stable or in the case of untreated or progressive lesions not mandating immediate local treatment intervention. Of note, tucatinib was generally well tolerated when combined with both trastuzuamb and capecitabine with low-grade adverse effects manifested in a small proportion of patients. The observed objective response rate increased from 23 to 41% across all subgroups with an overall reduction in risk of death by a third and risk of progression or death by half in the TKI arm. There was an increase in overall survival of 4.5 months from 17.4 months to 21.9 months and for those patients with brain metastases the median progression-free survival increased from 5.4 to 7.6 months. It was commented that HER2CLIMB is the 'most exciting study presented today' with the potential for tucatinib to become a new standard of care in HER2-positive MBC populations 'with' and 'without' brain metastases. Equally exciting were results from the DESTINY-Breast01 study presented by I Krop (Dana Farber Cancer Institute, MA, USA) in the same session. This open-label Phase II multicenter trial evaluated the drug conjugate T-DXd that is designed to deliver an optimal antitumor effect and has a different cytotoxic payload to T-DM1. Thus, while T-DM1 is a microtubule inhibitor conjugate, T-DXd is a potent topoisomerase I inhibitor and tumors may be less likely to develop resistance. This trial of T-DXd recruited 253 patients with either unresectable or MBC (or both) and prior treatment with T-DM1. Confirmation of HER2 status on central archival tissue was essential and brain metastases were not an exclusion criteria. A relatively high objective response rate of 61% (112/184 patients) was noted with an increase in median progression-free survival of 19 months that is two-threefold greater than the usual period of 4–5 months. Furthermore, there was durable benefit in heavily pretreated patients with 11 complete (6%) and 101 partial responses (54.9%). These preliminary data on a novel drug conjugate were described as 'fantastic' by C Arteaga (SABCS co-director). However, despite low-grade adverse effects there was notable occurrence of interstitial lung disease, some cases of which required corticosteroid treatment with four deaths recorded on trial.

Anti-HER2 strategies were further discussed in the Clinical Science Forum moderated by S Loibl (German Breast Group, Frankfurt, Germany) who reminded the audience of the heterogeneity of HER2 receptor expression at both the protein and mRNA levels. Median survival for patients with HER2-positive disease has doubled in recent years with first-line therapies based on trastuzumab and pertuzumab combined with a taxane. Second-line treatment to date has involved the prototype drug conjugate T-DM1 whose mechanism of action relies on inhibition of microtubule formation. These agents combine antigen specificity with potent cytotoxic effects in a single molecule and T-DM1 benefits MBC previously treated with anti-HER2 therapies is an effective adjuvant agent following induction chemotherapy in HER2-positive patients [10]. Another example is the aforementioned T-DXd (DS-8201) that is especially effective in HER2 lower expressing tumors and achieved disease control in 97% of cases in the DESTINY-Breast01 trial. The latter provided compelling efficacy data with manageable toxicity provided patients are monitored for interstitial lung disease. TKIs are small molecules that can cross the blood–brain barrier and a pan-HER inhibitor (neratinib) has been investigated for HER2-positive MBC in the NALA trial [11]. Tucatinib is another TKI inhibitor that spares HER1 and consequently is associated with less gastrointestinal and cutaneous toxicity. This agent could be combined with T-DM1 to treat brain metastases that hitherto have not been impacted by adjuvant anti-HER2 therapies.

APHINITY (BIG 4–11) is a randomized multicenter trial comparing chemotherapy with either dual (trastuzumab plus pertuzumab) or single anti-HER2 therapy (trastuzumab) as adjuvant therapy in operable early stage HER2-positive breast cancer [12]. This trial previously demonstrated a modest effect from addition of pertuzumab to trastuzumab as adjuvant targeted therapy with an increase of invasive disease-free survival from 90.6 to 92.3% with benefit mainly for node positive or hormone receptor negative disease. Nonetheless, despite these small absolute gains from dual treatment, there was a statistically significant improvement for invasive disease-free survival at interim analysis with a median follow-up of 45.4 months. M Piccard (Jules Bordet Institute, Brussels, Belgium) presented an updated analysis of trial data at 6 years follow-up (74.1 months) and confirmed there was a continued reduction in risk of recurrence and death among these HER2-positive patients. Significant fewer events occurred in the pertuzumab group (n = 221) compared with placebo (n = 287; HR: 0.85; p-value = ns) and the overall absolute benefit from dual anti-HER2 therapy was 2.8%. Benefits from addition of pertuzumab were proportionately much greater for node positive patients for whom the absolute benefit was 4.5%. It was emphasized that although no gain in survival was seen for node negative patients, this group nonetheless had an impressive overall survival of 95%. About 10% of patients discontinued pertuzumab due to troublesome diarrhea.

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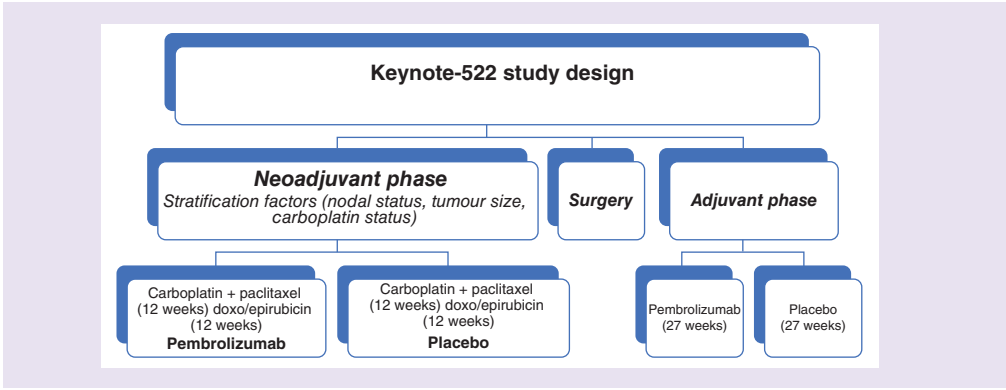

Figure 2. Schematic diagram showing design of the Keynote-522 study evaluating the addition of the immune checkpoint inhibitor pembrolizumab to upfront chemotherapy for early stage triple negative breast cancers.

Immunotherapy with checkpoint inhibitors

Previous Phase I and II studies have evaluated the combination of a checkpoint inhibitor (pembrolizumab) with chemotherapy as neoadjuvant therapy for locally advanced forms of TNBC. These have consistently demonstrated enhanced anti-tumor efficacy with a manageable side effect profile. Keynote-522 is a randomized study of pembrolizumab versus placebo plus chemotherapy as a neoadjuvant schedule, followed by pembrolizumab versus placebo as adjuvant treatment for early triple-negative breast cancer (n = 1174; Figure 2). Peter Schmid (Barts Cancer Institute, London, UK) presented results of this trial that showed significant improvement in rates of pCR from the addition of pembrolizumab to standard chemotherapy (difference in pCR = 13.6%; 64.8 vs 51.2%; p = 0.0050). Interestingly, the response to immunotherapy was not confined to PD-L1 positive tumors and significant benefit was observed for PD-L1 negative tumors. The extent of immune infiltration by lymphocytes in TNBC is related to prognosis and reflected by expression of PD-L1 [13]. Hence PD-1/PD-L1 blockade should enhance response to chemotherapy through immune modulation in those patients with PD-L1 positive tumors. Schmid surmised that due to innate plasticity of tumors, some might change from being PD-L1 negative at presentation with conversion to positivity after commencement of immunotherapy. A subgroup analysis of patients with lymph node involvement (~50%) revealed an even greater difference in pCR for pembrolizumab plus chemotherapy (64.8%) compared with placebo plus chemotherapy (44.1%). Furthermore, rates of response appear higher for patients with stage III disease and it was recommended that immunotherapy be considered for patients with more aggressive disease – whether this be TNBC or otherwise. Schmid reiterated that tumors are functionally dynamic in the early stages of carcinogenesis when immune cells can penetrate into the tumor bolus more readily. It is imperative that adequate numbers of immune cells be present and activated within a tumor in order to effectively kill cancer cells. K Osborne (Director SABCS) stated that use of immunotherapy remained 'in its infancy' for breast cancer patients but results to-date are intriguing. In contrast to Keynote-522, another study of similar design *prima facie* showed no benefit from addition of an immune checkpoint inhibitor. L Gianni (Milan, Italy) reported results from the NeoTRIP study that evaluated addition of a different checkpoint inhibitor (atezolizumab) to chemotherapy in a seemingly similar group of TNBC patients. This Italian trial found no difference in rates of pCR between immunotherapy (43.5%; 95% CI: 35.1–52.2) and placebo (40.8%; 95% CI: 32.7–49.4) groups (p = 0.66). However, although this trial also recruited higher stage patients, the precise selection criteria varied from Keynote-522. Moreover, PDL-1 may not necessarily be the best predictor of response to immunotherapy and potential long term toxicity (including 'financial toxicity') should be considered.

The SABCS 2019 featured work of many investigators not mentioned above but who have worked diligently to reduce the burden of breast cancer. More importantly, the symposium continues to demonstrate the courage of thousands of women around the world who have participated in clinical trials and contributed to advances in the field of both clinical and translational research. International collaboration will aid identification of biomarkers of response and help select those patients who benefit most from systemic interventions while allowing less intensive therapies in others with concomitant reduction of adverse side effects and improved quality of life. This strategy of de-escalation applies to both systemic and loco-regional treatments with surgery and radiotherapy, but robust data on clinical outcomes is essential before lesser forms of treatment become standard of care.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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